REMARKS/ARGUMENTS

The Examiner has rejected Claim 15 under 35 U.S.C. § 101 as directed to non-statutory subject matter. Claim 15 has been amended to specify that the claimed protein is a purified protein. Support for amendment of claim 15 can be found at p. 7, lines 32-37.

The Examiner has rejected Claim 15 under 35 U.S.C. § 112, second paragraph, as indefinite for reciting the pI of a membrane-bound protein in its "natural state." The Examiner takes the view that it is not possible to measure the pI of a protein in its natural location, that is, in a membrane. In response, the reference to "natural state" in the claim is not intended to specify the location at which pI of the protein is measured, but rather the condition of the protein when the measurement of pI is made. That is, the claim does not require that a measurement be made in situ, rather that after isolation, the protein remains in its natural condition when the measurement of pI is made. For example, the protein in its natural state is heavily glycosylated. The claim thus allows the measurement of pI to be made on the isolated protein but requires that it be made before the isolated protein has been exposed to any deglycosylation that might change the pI from that occurring in the natural state. This is in accordance with the Example showing measurement of pI provided in the specification. In light of this explanation and the Example, it is submitted that the reference to "natural state" in the claims is clear and as definite as the subject matter permits. It is noted that the same terminology was used in the issued parent patent. Accordingly, withdrawal of the rejection is respectfully requested.

The Examiner has rejected Claim 15 as anticipated under 35 U.S.C. § 102(b), or alternatively as obvious under 35 U.S.C. § 103(a), over Pak et al., Roep et al., and Ko et al.

Pak et al.

The Examiner has rejected Claim 15 as anticipated by, or in the alternative, obvious over a 38 kD protein described by Pak. However, the 38 kD antigen described by Pak is not the same protein claimed in pending Claim 15. Specifically, the Pak 38 kD antigen was found to be absent from human brain tissue (see Pak, p. 571, first column, first paragraph). By contrast, data

obtained by the inventors has demonstrated that the claimed 38 kD protein, know known in the scientific literature as Glima-38, is expressed in most brain tissue-derived neuronal and neuroblastoma cell lines (see Aanstoot, J Clin Invest. 1996 Jun 15;97(12):2772-83, Table I; cited on attached supplemental IDS). The different tissue expression patterns for the claimed 38 kD protein and the Pak antigen indicate that the two are different proteins. Furthermore, the Pak antigen obtained from the human pancreas was observed to run on an SDS-PAGE gel as a sharp band (see Fig. 2 of Pak). By contrast, the claimed 38 kD antigen obtained from any source has always been found to run as a diffuse band on SDS-PAGE gels, indicative of heterogeneous glycosylation (see specification at p.11, lines 35-37 and Figures 1 and 2). The different appearance of the respective bands under SDS-PAGE provides further evidence that the bands represent different proteins. These distinctions are described in more detail in the attached declaration of Dr. Beakkeskov, originally filed in the parent case that led to U.S. Patent 6,316,209. For these reasons, Pak's antigen is not the same protein as that claimed.

Roep et al.

The Examiner has rejected Claim 15 as anticipated by, or in the alternative, obvious over a 38 kD protein identified by Roep et al. (the "Roep 1991" reference). The Roep 1991 reference discusses a 38 kD antigen that stimulates proliferation of CD4 T cells. This antigen was prepared from insulin secretory granules from a beta-cell tumor. The Roep 1991 reference presents follow-up work from an earlier publication by Roep that tentatively assigned a molecular weight of 38 kD to the antigen that causes the T cell activation (Roep et al., Nature. 1990 Jun 14;345(6276):632-4; referred to as the "Roep 1990" reference). An activated T cell clone from the Roep 1990 reference (referred to as the "1C6 clone") was used to map a peptide identified from an expression library that encodes an approximately 38 kD protein (Neophytou et al., Proc Natl Acad Sci U S A. 1996 Mar 5;93(5):2014-8; copy enclosed). The 38 kDa protein that stimulates proliferation of the T cell clone, first examined in Roep 1990, then in Roep 1991 (cited by the Examiner), and partially identified in Neophytou, was eventually completely isolated, sequenced, and named Imogen-38 (Arden et al., J Clin Invest. 1996 Jan 15;97(2):551-61; copy enclosed).

Several lines of evidence distinguish Imogen-38 from Glima-38. First, Glima-38 possesses N-linked glycosylation and drops in size from 38 kD to 22 kD upon treatment by N-glycanase (see Fig. 4 of Aanstoot). By contrast, the gene encoding Imogen-38 has no N-glycosylation consensus sequences and predicts a 44 kD protein. When translated *in vitro*, a 44 kD protein is produced by the Imogen-38 gene. When the gene is expressed in cells, Western blot analysis detects an approximately 38 kD protein (Arden, Fig. 6). Therefore, Imogen-38's approximate 38 kD weight results from processing of a larger 44 kD protein. By contrast, Glima-38's 38 kD weight results from addition of carbohydrate groups to a 22 kD protein. Second, Imogen-38 was detected in all tissues examined (Arden, Figure 8). By contrast, Glima-38's tissue distribution is relatively narrow (Aanstoot, Table I). Third, Imogen-38 is solubilized by sonication (Arden, p. 559, top of second column), whereas Glima-38 is only isolated after "vigourous 2 hour extraction of islet cell membranes". (Aanstoot, second paragrapoh of Results section). Finally, the claimed protein has a pI range in its natural state of 5.4 to 6.1, whereas that of Imogen-38 is from 8.0 to 7.1 (Arden, p. 559, first column, last paragraph).

These distinctions are described in more detail in the Aanstoot paper:

> The 38-kD antigen is distinct from two diabetes-associated antigens of similar apparent molecular mass previously described, jun B and imogen 38. Its cellular expression pattern differs from that of imogen 38, which was identified as a target of a $CD4^+$ T cell clone derived from a type 1 diabetic patient and has a wide tissue distribution. Furthermore, imogen 38 is not N-asp glycosylated and does not seem to be a target of humoral autoantibodies in type 1 diabetes.
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> Aanstoot, p. 2781, second column, third paragraph.

The preceding evidence shows the approximately 38 kD protein described in Roep 1991 is not the same as the presently claimed protein.

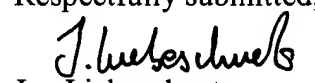
Ko et al.

The examiner has cited Ko as disclosing a 38 kD autoantigen in diabetes-prone rats. Figures 1, 2, and 4 of Ko show that the antigen migrates as a sharp band on SDS-PAGE gels. As mentioned previously, the claimed 38 kD antigen obtained from any source has always been found to run as a diffuse band on SDS-PAGE gels, indicative of heterogeneous glycosylation (see specification at p.11, lines 35-37 and Figures 1 and 2). These data again demonstrate that Ko's antigen is a different protein that Glima-38. This conclusion is supported by experimental evidence from Dr. Baekkeskov's laboratory (see attached declaration). Dr. Baekkeskov obtained ten BB-rat serum samples that react with the Ko antigen from Dr. Yoon, the senior and responsible author of the Ko paper. None of the serum samples recognize the glima-38 antigen, indicating that the two are different proteins.

For these reasons the 38 kDa protein recited in the present claims is a different protein than proteins of similar molecular weight referred to in the references by Ko, Roep, and Pak.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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